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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/286,874	04/06/99	GRAHAM F	ADVEC9

HM12/1024

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EXAMINER	
BRUNOVSKIS,P	
ART UNIT	**PAPER NUMBER**
1632	8

DATE MAILED: 10/24/00

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trad marks

Office Action Summary	Application No. 09/286,874	Applicant(s) Graham et al.
	Examiner Peter Brunovskis	Group Art Unit 1632

☒ Responsive to communication(s) filed on *Aug 25, 2000*

☐ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *3* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claim

☒ Claim(s) *1-14* is/are pending in the applicat

Of the above, claim(s) *5-7 and 10-12* is/are withdrawn from consideration

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *1-4, 8, 9, 13, and 14* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☒ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☒ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____ .

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). *4, 5*

☐ Interview Summary, PTO-413

☒ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

DETAILED ACTION

Election/Restriction

Applicant's election with traverse of Group I , claims 1-4, 8, 9, 13, and 14 in Paper No. 7, filed 8/25/00 is acknowledged. The traversal is on the ground(s) that alleged relatedness of the subject matter of the two groups of claims, such that searching the claims of the first group of claims will necessarily lead the Examiner to consider similar art to determine the patentability of each set of claims. It is further argued that in spite of the examiner's assertion that "the adenoviral vector of Invention I [is] is not limited in the processes cited in Invention II and can be used for in vitro cell transfection assay and/or production of stocks of replication defective adenoviral particles, it is urged that these claims should nonetheless be examined in the same application and issued to patent at the same time" essentially because the public would be better served by being informed as to the subject matter that the applicant considers to be their invention and to make evident the metes and bounds of the patented technology. This is not found persuasive because the arguments concerning alleged benefits to the public are not probative and because the inventions of groups I and II have separate classifications requiring different searches that are not co-extensive. For example, the methods of Group II utilize embodiments that are broader in scope compared to the embodiments of Group I that would not necessarily be identified if conducting a search of the invention of Group I.

The requirement is still deemed proper and is therefore made FINAL.

Priority

Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. 120 as follows:

> The second application (which is called a continuing application) must be an application for a patent for an invention which is also disclosed in the first application (the parent or provisional application); the disclosure of the invention in the parent application and in the continuing application must be sufficient to comply with the requirements of the first paragraph of 35 U.S.C. 112. See *In re Ahlbrecht*, 168 USPQ 293 (CCPA 1971).

There is no support in any of the parental applications for the claimed subject matter of the instant invention.

Information Disclosure Statement

WO 93/19191, WO 93/06223, and WO 93/19092 were only considered with respect to the English abstract, since no translations were supplied.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-4, 13, and 14 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 is rendered indefinite by its recitation of the term "substantially devoid" since it is unclear how this term is defined or what its metes and bounds are.

Claim 13 is indefinite by its recitation of the phrases, "ensure efficient expression...and efficient packaging in part (b) and "essentially no infectious particles of helper virus" in part (c) since it is unclear how these phrases are defined or what their metes and bounds are.

Claim 13 recites the limitation ""capsid proteins encoded by said helper adenovirus" in part (c). There is insufficient antecedent basis for this limitation in the claim.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-4, 8, 9, 13, and 14 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for making and using hdAd and helper adenoviral compositions wherein the genomes of hdAd or the helper adenovirus are from Ad-2 or Ad-5, does not reasonably provide enablement for making and using hdAd or helper adenoviruses encoding capsid proteins from any and all adenoviral serotypes. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make

the invention commensurate in scope with these claims. The specification states that "[o]ver 40 different serotypes of human Ads have been isolated, suggesting that, in theory, Ad vectors of different serotypes could be administered many times throughout the life of a patient" (emphasis added; p. 3, lines 20-22). However, the specification only describes working examples using serotype 2 (Ad2) and serotype 5 (Ad5) helper adenoviruses and Ad2- and Ad-5-based floxed helper dependent adenoviral vectors. Both of these serotype are from the same closely related subgroup type. However, the specification does not provide sufficient guidance teaching which adenoviral serotype ITRs or packaging signals can be complemented or recognized by which heterologous adenoviral capsid serotypes. There is no information provided to suggest broad complementation between any and all adenoviral ITRs and capsids to the degree embraced by the instant claims. Such complementation would appear highly unpredictable because it is not routinely performed in the art and there is no expectation of success in mixing or matching any of the 40+ adenoviral serotype capsid and ITR/packaging site elements from different and distinct groups (e.g. Group A, -B, -C, -D, -E) with one another to form infectious particles--especially wherein the series of "genetically identical adenoviral vectors" have different capsid serotypes.

At least 47 different serotypes have been identified thus far. These have been divided into 6 subgenera (A-F) based on various parameters, including tissue tropism (Bailey et al., Virol., 205:438-452, 1994). Bailey has previously reported that "a diverse tissue tropism exists within the human adenoviruses...but little is known about the mechanisms at the molecular level which determine this tropism...and little is known about the interrelationship between the different

subgenera" (p. 438, right col.). Although the Ad2 and Ad5 are highly conserved subgenera C-type human adenoviruses, they nevertheless share three related regions (hexon, E3, and fiber) subject to more rapid change than the rest of the genome (p. 447, left col.). Furthermore, the coding potential of the enteric viruses Ad40 and Ad12 differs markedly from the other subgenera (p. 448, left col.). The working example in the specification are limited to C-type adenoviruses which are normally observed in persistent infections of the adenoids and tonsils, although there is frequently an association with respiratory disease (Bailey, p. 438, left col.). It is noted that the subject matter in the claims includes kits comprising hdAd vectors and a series of helper adenoviruses of essentially any different serotype. However, the specification does not provide sufficient guidance teaching how to use different serotypes sequentially, wherein for example, the serotypes share limited or no tissue tropism with one another. Moreover, the specification does not teach which subgenera ITRs (including origins of replication) or packaging signals can be recognized or functionally complemented by what breadth of adenoviral serotype helper functions. Importantly, it is noted that such adenovirus functions are not interchangeable. For example, Hay has previously reported that the ori activity of the Ad4 ITR is very low with Ad2 helper (5% homologous level; J. Mol. Biol., 186:129-136, 1985, p. 135, middle, right col.). Temperley et al. have further shown that the proteins required for DNA replication differ markedly between Ad2 and Ad5 and Ad4 in that Ad2 and Ad5 are dependent on the host factors NFI/CTF and NFIII/oct-1 for efficient DNA replication (J. Virol., 65(9):5037-5044, 9/1991, p. 5037, right col.). However, in view of these observations, it is important to note that the specification does not

provide e.g. a sufficient basis or adequate guidance concerning the sequential use of e.g. hdAd Ad2/Ad5 virus vectors followed by introduction of hdAd virus of Ad4 (subgenera E) which would not necessarily have the same tropism or same levels of cellular transcription factors for efficient replication. It is further noted that work by Thorner et al. has established there to be significant genomic variability within the subgenus A (Arch. Virol., 133:397-405, 1993, p. 403). Moreover, Hearing et al. have taught that conserved cis-acting regions of Ad3, Ad7, and Ad12 contain a single copy of sequence homologous (yet not identical) to the Ad5 "A segment", though the corresponding region of Ad3 does not appear to play a role in packaging (J. Virol., 61(8):2555-2558, 8/1987; p. 2558, left col.). Further, Hearing argued that "[s]ince the protein that recognizes the packaging signal is likely coded by the virus, it might be argued that the factor and binding site have coevolved rapidly and the sequences which signal packaging in different adenovirus serotypes have drifted considerably (p. 2558, left col.). Additionally, Klimkait et al. have reported that despite the ability of Ad12 functions to effectively complement E1A or to a lesser extent E1B deletions in the Ad5 genome in hamster cells, the same can not be said of Ad5 E1A or E1B in complementing the deficient late Ad12 protein synthesis in hamster cells (Virol., 161:109-120, 1987; see abstract). In view of the different structural properties among adenoviral genomes generally (especially between human and nonhuman), between different human subgeneras specifically, and given the lack of information defining the degree of functional conservation between any given subgenera, these observations suggest the unpredictability associated with mixing and matching adenoviral *cis* and *trans* functions from

different serotypes in the absence of trial and error experimentation requiring undue experimentation.

Conclusion

The closest prior art drawn to Applicants claimed invention is provided by Mack et al (Hum. Gene Ther., 8:99-109, 1/1997) which teaches circumventing anti-adenoviral neutralizing immunity by sequentially readministering adenoviral vectors packaged with an alternate serotype (e.g. Ad-5 followed by Ad-2). However, Mack does not teach sequential readministration using a series of genetically identical hdAd derived from a series of helper adenoviruses of differing serotypes, nor does Mack teach the ability of different serotypes of helper adenoviruses to complement the same (i.e. genetically identical) hdAd genome, nor suggest making or rendering obvious the readministration of *gutless* hdAd adenoviral vectors of different serotypes, or providing a basis for complementing defective Ad2 or Ad5-based vectors with anything more than a limited portion of the Ad5 genome contained in 293 cells complementing an defect in E1 functions.

Certain papers related to this application may be submitted to Art Unit 1632 by facsimile transmission. The FAX number is (703) 308-4242 or 305-3014. The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 CFR 1.6(d)). NOTE: If applicant *does* submit a paper by FAX, the original copy should be retained by applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED, so as to avoid the processing of duplicate papers in the Office.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Peter Brunovskis whose telephone number is (703) 305-2471. The examiner can normally be reached on Monday through Friday from 8:30 AM to 5 PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Karen Hauda can be reached at (703) 305-6608.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Peter Brunovskis, Ph.D.
Patent Examiner
Art Unit 1632

Scott D Priebe

SCOTT D. PRIEBE, PH.D
PRIMARY EXAMINER